Chemistry of Heterocyclic Compounds, Vol. 41, No. 4, 2005

CHEMICAL REACTIONS OF 2-METHYL-5,7-DIPHENYL-6,7-DIHYDRO-PYRAZOLO[1,5-*a*]PYRIMIDINE

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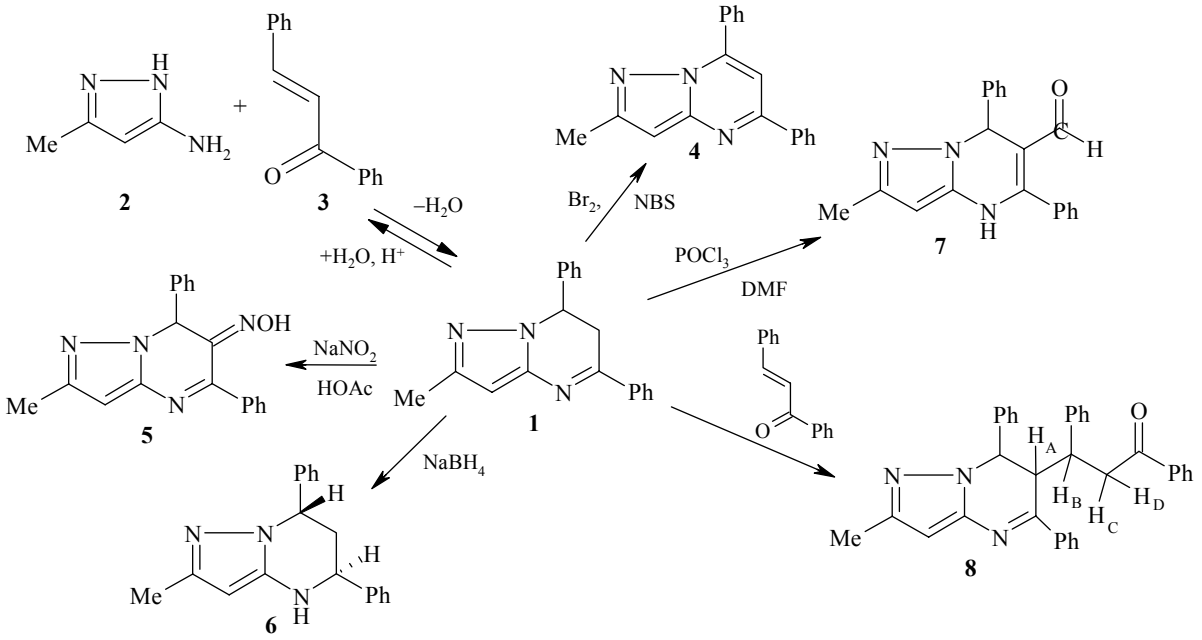
The hydrolysis, oxidation, reduction, alkylation, formylation, and nitrosation reactions of 2-methyl-5,7-diphenyl-6,7-dihydropyrazolo[1,5-a]pyrimidine have been studied.

Keywords: dihydropyrimidine system, acylation, alkylation, hydrolysis, reduction, nitrosation, oxidation.

The dihydropyrimidine system in 2-methyl-5,7-diphenyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidine **1** is a convenient model for investigation of the reactivity, chemical stability, and tautomerism of partially hydrogenated azoloazines. The synthesis of compound **1**, its tendency to oxidation in solutions to form a 6-hydroxy derivative, and the stability of the latter to the action of dehydrating agents have been reported before [1]. In this work we have studied the hydrolysis, oxidation, reduction, nitrosation, formylation, and alkylation of the dihydropyrazolo[1,5-*a*]pyrimidine **1**.



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 0009-3122/05/4104-0492

The behavior of compound **1** has been investigated. It is almost completely hydrolyzed to give the aminopyrazole **2** and unsaturated ketone **3** when heated in hydrochloric acid (1:1) for 30 min.

In the presence of N-bromosuccinimide in alcohol or Br_2 in acetic acid dehydrogenation of the dihydropyrazolopyrimidine **1** to compound **4** occurs, the parameters of which have been previously reported in [1].

It is known that 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine in the presence of sodium nitrite in glacial acetic acid forms a hydroximino derivative [2], in contrast to the dihydropyridines which undergo heteroaromatization [3] under similar conditions. The dihydropyrazolopyrimidine **1** can also be nitrosated to form the oxime **5**. An absorption band for the –C=C– bond is absent in the IR spectrum of compound **5** (Table 1) and this rejects a corresponding N-nitroso derivative structure. The ^{1}H NMR spectrum of compound **5** (Table 2) shows, beside a multiplet for the aromatic protons and singlets for the methyl group and pyrazole ring methine protons, a singlet for the $C_{(7)}$ proton and a broadened singlet signal for the OH group. As a whole, the spectrum resembles that of the 2-aza analog of **5**, the structure of which was demonstrated by X-ray investigation [2, 4, 5].

Reduction of the dihydropyrazolopyrimidine **1** with sodium borohydride gives the tetrahydro derivative **6**. Bearing in mind that the molecule of compound **6** has two chiral centers there arises the question of the stereoselectivity of the process of its formation. The answer comes from analysis of the ^{1}H NMR spectra. The spectra, including that of the uncrystallized reduction product of **6**, show a single isomer and point to the stereoselectivity of the indicated reaction. Signals for the methine and methylene protons of the tetrahydropyrimidine ring are identified in it. The assignment of the $C_{(5)}$ and $C_{(7)}$ proton signals was based on a comparison of these spectra with data [2, 6] for the spectra of the 3-aza analogs of compound **6**, according to which the $C_{(5)}$ proton resonates at higher field. The values of $J_{HB\text{-}5H}$ and $J_{HB\text{-}7H}$ are 11.1 and 10.9 Hz and are characteristic of a J_{aa} type constant and so point to a diequatorial orientation of both phenyl substituents in the tetrahydropyrimidine ring. Hence compound **6** can be assigned to a trans isomer series.

An attempt to formylate the dihydropyrazolopyrimidine **1** under Vilsmeier conditions (DMF–$POCl_3$) led to formation of the aldehyde **7**. The structure of the product **7** was proved by the following spectroscopic data. The IR spectrum showed absorption bands for the carbonyl group ν_{CO} at 1652 cm^{-1} and a pyrimidine ring –C=C– bond at 1620 cm^{-1}. The presence in the ^{1}H NMR spectrum (see Table 2) of singlets for the NH and $C_{(7)}$ protons and signals for the protons of the pyrazole ring methine, phenyl, methyl, and formyl substituents unambiguously pointed to formylation at position 6 of the bicycle. It should be noted that dihydropyrazolo-[1,5-*a*]pyrimidines, including compound **1**, both in solutions and in the solid phase, usually exist in the imine 6,7-dihydro form [1, 7]. However, in the case of the aldehyde **7** the introduction of an electron-acceptor substituent at position 6 of the bicycle leads to a complete transfer to the enamine 4,7-dihydro form.

TABLE 1. Parameters for the Compounds Synthesized

Com-pound	Empirical formula	Found N, % / Calculated N, %	mp, °C	IR spectrum (KBr), ν, cm^{-1}	Yield, %
5	$C_{19}H_{16}N_4O$	17.75 / 17.71	289*	3300-2500, 1556	91
6	$C_{19}H_{18}N_3$	14.57 / 14.53	108*	3624, 3284, 3152-2800, 1648, 1576	70
7	$C_{20}H_{17}N_3O$	13.36 / 13.32	178-180	3448, 1652, 1620, 1536	71
8	$C_{34}H_{29}N_3O$	8.51 / 8.48	179-181	3064, 3036, 2908, 1684, 1620, 1564	52

* Melted with decomposition.

TABLE 2. ^{1}H NMR Spectra of Compounds **5-8**

Compound	Chemical shifts, δ, ppm, spin-spin coupling (*J*, Hz) (DMSO-d_6)				
	NH (OH) (1H, br. s)	H_{Ar}, m	CH	CH_2	CH_3 (3H, s)
5	13.1	7.1-7.7 (10H)	C(3)H: 6.71 (1H, s); C(7)H: 6.36 (1H, s)	—	2.14
6	5.2	7.2-7.5 (10H)	C(3)H: 6.27 (1H, s); C(7)H: 5.25 (1H, dd, J_{7A} = 5.2, J_{7B} = 10.9); C(5)H: 4.56 (1H, d, J_{5A} = 2.5, J_{5B} = 11.1)	H_A: 2.35 oct, H_B: 2.03 oct, J_{AB} = -13.4	1.94
7	10.2	7.0-7.5 (10H)	C(H)O: 9.02 (1H, s); C(3)H: 6.19 (1H, s); C(7)H: 5.91 (1H, s)	—	2.63
8	—	6.7-8.1 (20H)	C(3)H: 5.94 (1H, s); C(7)H: 5.62 (1H, s); C(6)H_A: 4.10 (1H, d.d); H_B: 3.52 (1H, dd, J_{AB} = 6.1)	H_C: 3.94 (1H, dd, J_{CD} = -17.8, J_{CB} = 7.8); H_D: 3.57 (1H, m*, J_{DB} = 5.0)	2.08

* Partially obscured by the H_B signals.

In the case of dihydropyridines it has been shown that, depending on the conditions for carrying out the reaction, their alkylation can occur both at a nitrogen and at a carbon atom [8]. We have previously found that dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines are alkylated in basic media both by methyl iodide and by dimethylsulfate exclusively at a pyrimidine ring nitrogen atom [2]. When using analogous reaction conditions the alkylation of the dihydropyrazolopyrimidine **1** gave a mixture of oily materials which were hard to identify. However, refluxing of the discussed compound with benzalacetophenone **3** in methanol in the presence of sodium methylate gave the product **8** which was shown to be 3-(2-methyl-5,7-diphenyl-6,7-dihydropyrazolo-[1,5-*a*]pyrimidin-6-yl)-1,3-diphenylpropanone on the basis of the following spectroscopic data. The IR spectrum showed an absorption band for ν_{CO} at 1684 cm^{-1}. The ^{1}H NMR spectrum showed a phenyl substituent multiplet with an integrated intensity corresponding to 20 protons. In addition, it showed singlets for the pyrazole $C_{(3)}$ and pyrimidine $C_{(7)}$ ring methine protons as well as signals for a four spin system formed by the $C_{(6)}H_A$ and CH_B–CH_2(CD) protons of the propanone fragment. The absence of a signal for an NH group proton and the presence of signals for C_6H_A forming an AB system with the propanone fragment methine proton points to the existence of compound **8** in the imine 6,7-dihydro form.

EXPERIMENTAL

IR spectra were recorded on a Specord M-82 spectrometer for KBr tablets and ^{1}H NMR spectra on a Varian-200 (200 MHz) spectrometer using DMSO-d_6 and TMS internal standard. Monitoring of the composition of the reaction mixtures and the purity of the compounds obtained was carried out using TLC on Silufol UV-254 plates with benzene–methanol (10:1) or ethanol–chloroform–hexane (1:1:1) eluent.

Hydrolysis of 2-Methyl-5,7-diphenyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidine (1). Compound **1** (0.57 g, 2 mmol) in HCl (1:1, 20 ml) was refluxed for 30 min, neutralized using saturated Na_2CO_3 solution, and extracted with chloroform. The extract was dried over anhydrous Na_2SO_4. Removal of solvent gave the

benzalacetophenone **3** (0.38 g, 92%); mp 59°C (ethanol) [9]). TLC showed that the aqueous layer after extraction contained 3-amino-5-methylpyrazole **2** (R_f 0.44), eluent ethanol–chloroform–hexane, 1:1:1.

Oxidation of 2-Methyl-5,7-diphenyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidine (1). A. A solution of bromine (0.7 g, 4.4 mmol) in acetic acid (2 ml) was added to a solution of compound **1** (1.15 g, 4 mmol) in acetic acid (15 ml). The product was stirred for 1 h and the reaction mixture was poured into water and filtered to give compound **4** (0.98 g, 86%); mp 110-112°C (from 2-propanol) [1].

B. N-Bromosuccinimide (0.62 g, 3.5 mmol) was added to a solution of compound **1** (0.86 g, 3 mmol) in 2-propanol and refluxed with a reflux condenser for 1 h. Pouring into water, neutralizing with saturated $NaHCO_3$ solution, and filtration gave the product **4** (0.77 g, 90%).

6-Hydroximino-2-methyl-5,7-diphenyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidine (5). Sodium nitrite (0.37 g, 5.3 mmol) was added in about 0.1 g portions to a solution of compound **1** (1.15 g, 4 mmol) in acetic acid (15 ml). At the end of the evolution of gaseous products the reaction mixture was poured into water and filtered to give compound **5** (1.15 g) which was crystallized from ethanol.

2-Methyl-5,7-diphenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine (6). $NaBH_4$ (1.52 g, 40 mmol) was added to a suspension of compound **1** (1.15 g, 4 mmol) in methanol (10 ml). At the end of the evolution of gaseous products the reaction mixture was refluxed with a reflux condenser for 20 min, poured into water, and filtered to give compound **6** (0.81 g) which was crystallized from methanol.

2-Methyl-5,7-diphenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carbaldehyde (7). $POCl_3$ (0.32 ml, 3.5 mmol) was added to a solution of compound **1** (0.86 g, 3 mmol) in DMF (3 ml) at 5-10°C. The reaction mixture was gradually heated, held on a refluxing water bath for 3 h, poured onto ice, neutralized with 20% NaOH solution, and filtered to give compound **7** (0.67 g) which was crystallized from methanol.

3-(2-Methyl-5,7-diphenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)-1,3-diphenylpropanone (8). A solution of sodium methylate (0.05 g, 2.2 mmol), compound **1** (0.32 g, 1.1 mmol), and benzalacetophenone **3** (0.25 g, 1.2 mmol) in methanol (10 ml) was refluxed with a reflux condenser for 2 h. After cooling, the reaction mixture was filtered off to give compound **8** (0.29 g) which was crystallized from ethanol.

This work was carried out with the support of the Ukraine Fund for Fundamental Research (project No. 0307/00154).

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